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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/973,375	10/09/2001	Donald Gerald Stein	07157/239838 (5543-17)	5877

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EXAMINER	
JIANG, SHAOJIA A	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 06/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/973,375	STEIN ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005 and 18 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicant's amendment and response filed on April 7, 2005 and February 18, 2005 wherein claim 13 is cancelled and claims 1-12 and 14-20 have been amended.

Currently, claims 1-12 and 14-20 are pending in this application.

Claims 1-12 and 14-20 as amended now are examined on the merits herein.

Applicant's amendment filed on April 7, 2005 and February 18, 2005 with respect to the rejection made under 35 U.S.C. 112 second paragraph for the use of the indefinite recitation "a subject" of record stated in the Office Action dated November 4, 2004 have been fully considered and found persuasive to remove the rejection since the claims have been amended to remove the indefinite recitations. Therefore, the said rejection is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-12 and 15-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Roof et al., (*Molecular and Chem. Neuropathology*, 1997, vol.31, 1-11) for same reasons of record stated in the Office Action dated November 4, 2004.

Roof et al. discloses that progesterone has been shown to have neuroprotective effects following traumatic brain injury in rat patients, and/or in injured nervous system including the severity of postinjury cerebral edema in rat patients. See the entire article especially abstract and introduction. Roof et al. particularly discloses the administration of progesterone to male rat patients after suffering medical frontal cortex contusions, i.e., initial treatment of progesterone with a pharmaceutical carrier, oil, by injection, 4 mg/kg, was given 5 min post-injury and the remaining injections, 4 mg/kg, were given 6 hour post-injury and again once each 24-hours (see the last paragraph of page 3 to page 4 the 3rd paragraph), or the initial treatment after injury occurs at least within 2 hours of contusion (see page 6-7). Roof et al. also teaches that other agents or compounds such as vitamin E and methylprednisolone are known to be useful in the claimed method with progesterone (see page 3, lines 5-9).

Note that Roof et al. discloses that the effective amount of progesterone to be administered is in the range of 4 mg/kg, which is the instant claimed amount in claim 8 herein and also within the claimed effective amounts, about 1 μg/kg- 50 mg/kg, in claim 7 herein.

Given the fact that allopregnanolone is an old and well-known progesterone metabolite, which was necessarily produced in the patient's body upon ingestion of progesterone in the body (see "Steroid metabolism in humans" by Dobriner et al., e.g., page 48, of record), Roof's steps are thus inherently same as the instant method steps, administering progesterone which was necessarily converted to allopregnanolone in the

patient's body upon ingestion, in the same amount to the same patient population. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

Note that the court ruled that the metabolite of loratadine called descarboethoxyloratadine or "DCL" was INHERENTLY anticipated by loratadine (Claritin ™) because it was necessarily produced in the patient's body upon ingestion of Claritin ™. See Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003).

Moreover, Roof's method inherently decreases neurodegeneration in a patient following a traumatic injury to the central nervous system, as claimed herein since again Roof's method steps are same as the instant method steps, as discussed above.

Thus, Roof et al. anticipates Claims 1-12 and 15-20.

Claims 1-12 and 15-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Roof et al. (*Restoration Neurology and Neuroscience*, 1992, vol.4, 425-427) for same reasons of record stated in the Office Action dated November 4, 2004.

Roof et al. discloses that progesterone is useful in treating brain edema resulting from traumatic brain injury or following contusion injury in male and female rat patients. See the entire article especially abstract and introduction. Roof et al. particularly discloses the administration of progesterone with a pharmaceutical carrier, peanut oil, to male rat patents after suffering medical frontal cortex contusions, i.e., initial treatment of progesterone by injection, 4 mg/kg, was given 1 hour after contusion and the remaining

injections, 4 mg/kg, were given 6, 24 and 48 hour post-injury (see the 3rd paragraph of page 426), or the initial treatment after injury occurs at least within 2 hours of contusion (see page 6-7).

Note that Roof et al. discloses that the effective amount of progesterone to be administered is in the range of 4 mg/kg, which is the instant claimed amount in claim 8 herein and also within the claimed effective amounts, about 1 μg/kg- 50 mg/kg, in claim 7 herein.

Given the fact that allopregnanolone is an old and well-known progesterone metabolite, which was necessarily produced in the patient's body upon ingestion of progesterone in the body (see "Steroid metabolism in humans" by Dobriner et al., e.g., page 48, of record), Roof's steps are thus inherently same as the instant method steps, administering progesterone which was necessarily converted to allopregnanolone in the patient's body upon ingestion, in the same amount to the same patient population, as discussed above. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). See also Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003).

Moreover, Roof's method inherently decreases neurodegeneration in a patient following a traumatic injury to the central nervous system, as claimed herein since again Roof's method steps are same as the instant method steps, as discussed above.

Thus, Roof et al. anticipates Claims 1-12 and 15-20.

Response to Argument

Applicant's arguments filed April 7, 2005 and February 18, 2005 with respect to these rejections made under 35 U.S.C. 102(b) as being anticipated by Roof et al. in the previous Office have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art as further discussed below.

Applicant argues that "none of these references by Roof et al. teach or suggest the administration of allopregnanolone to treat a traumatic CNS injury or reduce neurodegeneration following a traumatic CNS injury".

Nonetheless, as discussed in the previous Office Action, Roof et al. discloses that progesterone has been shown to have neuroprotective effects following traumatic brain injury in rat patients, and/or in injured nervous system including the severity of postinjury cerebral edema in rat patients. See the entire article especially abstract and introduction. Roof et al. particularly discloses the administration of progesterone to male rat patients after suffering medical frontal cortex contusions, i.e., initial treatment of progesterone with a pharmaceutical carrier, oil, by injection, 4 mg/kg, was given 5 min post-injury and the remaining injections, 4 mg/kg, were given 6 hour post-injury and again once each 24-hours (see the last paragraph of page 3 to page 4 the 3rd paragraph), or the initial treatment after injury occurs at least within 2 hours of contusion (see page 6-7).

Allopregnanolone is an old and well-known progesterone metabolite, which was necessarily produced in the patient's body upon ingestion of progesterone in the body

(see "Steroid metabolism in humans" by Dobriner et al., e.g., page 48, of record), Roof's steps are thus inherently same as the instant method steps, administering progesterone which was necessarily converted to allopregnanolone in the patient's body upon ingestion, in the same amount to the same patient population. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993).

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 102(b). Therefore, said rejection is adhered to.

Claims 1-7 and 16-17 rejected under 35 U.S.C. 102(b) as being anticipated by Gee et al. (Re. 35,517) for same reasons of record stated in the Office Action dated November 4, 2004.

Gee et al. discloses that progesterone metabolites including the particular progesterone metabolite, allopregnanolone, are useful in a method for treating seizure disorders in a patient in need thereof (see particularly col.4 lines 37-39; col.1 lines 17-21; Table 2 at col.13-14). Gee et al. also discloses that the beneficial effect of progesterone is related to the conversion of progesterone to the active metabolites including allopregnanolone since the metabolites and derivatives possess higher potency and efficacy than progesterone (see col.17 lines 29-35).

Note that seizures are known to be resulted from traumatic brain injury (see Hernandez et al., *Seizures, epilepsy, and functional recovery after traumatic brain injury: a reappraisal*, of record).

Gee et al. also discloses the effective amounts of progesterone derivatives, either singly or *mixtures*, to be administered, i.e., 50 mg to 500 mg per dosage unit, and various known pharmaceutical carriers broadly in the compositions. See col.9 lines 16-25 and 32-62, col.10 lines 2-3, and claims 1 and 5.

Since a standard person weight is 70 kg, the claimed effective amount of about 1 μg/kg- 50 mg/kg, for example, 1 mg/kg X 70 kg =70 mg, within the Gee's range.

Thus, Gee's method steps are same as the instant method steps, administering the same compound in the same amount to the same patient population having seizures after traumatic brain injury. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3d. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001).

Thus, Gee et al. anticipates Claims 1-7 and 16-17.

Response to Argument

Applicant's arguments filed April 7, 2005 and February 18, 2005 with respect to this rejection made under 35 U.S.C. 102(b) as being anticipated by Gee et al. in the previous Office have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art as further discussed below.

Applicant argues that "Gee et al. does not teach the administration of allopregnanolone to a subject following a traumatic brain injury and accordingly a distinct population is being treated" (emphasis originally). Applicant's argument is not found persuasive. As discussed in the previous Office Action, Gee et al. discloses that progesterone metabolites including the particular progesterone metabolite,

allopregnanolone, are useful in a method for treating seizure disorders in a patient in need thereof.

Note that seizures are known to be resulted from traumatic brain injury (see Hernandez et al., *Seizures, epilepsy, and functional recovery after traumatic brain injury: a reappraisal*, of record).

Gee et al. also discloses the effective amounts of progesterone derivatives, either singly or *mixtures*, to be administered, i.e., 50 mg to 500 mg per dosage unit, and various known pharmaceutical carriers broadly in the compositions. See col.9 lines 16-25 and 32-62, col.10 lines 2-3, and claims 1 and 5.

Thus, Gee's method steps are same as the instant method steps, administering the same compound in the same amount to the same or similar or substantially overlapping patient population having seizures after traumatic brain injury.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 102(b). Therefore, said rejection is adhered to.

Claims 1-7 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Tauboll et al. (*Epilepsy Research*, (1993), 14(1), 17-30) for same reasons of record stated in the Office Action dated November 4, 2004.

Tauboll et al. discloses that progesterone and the particular progesterone metabolite, 5α-pregnan-3α-ol-20-one (3α-OH-DHP, also known as allopregnanolone) with a pharmaceutical carrier, glycofurol, are useful in a method for treating epileptic seizure in mammal patients such as cats (see abstract and the entire article).

Note that traumatic brain injury is known to cause epileptic seizure as discussed above (see Hernandez et al., *Seizures, epilepsy, and functional recovery after traumatic brain injury: a reappraisal*).

Tauboll et al. also discloses the effective amounts of 3α-OH-DHP, to be administered, i.v. injection 1.0 mg/kg (see abstract), or (0.5-1.0 mg/ml) X (0.13-0.4 ml/kg) (see the left column of page 19), within the instant claimed range.

Thus, Tauboll's method steps are same as the instant method steps, administering the same compound in the same amount to the same patient population of those having seizures after traumatic brain injury. See *Ex parte Novitski*, 26 USPQ 2d 1389, 1391 (Bd. Pat. App. & Int. 1993). See also *Eli Lilly and Co. v. Barr Laboratories Inc.* 251 F3d. 955; 58 USPQ2d 1869-1881 (Fed. Cir. 2001).

Thus, Tauboll et al. anticipates Claims 1-7 and 12.

Response to Argument

Applicant's arguments filed April 7, 2005 and February 18, 2005 with respect to this rejection made under 35 U.S.C. 102(b) as being anticipated by Tauboll et al. in the previous Office have been fully considered but they are not deemed persuasive to render the claimed invention patentable over the prior art as further discussed below.

Applicant argues that "Tauboll et al. did not teach a "physical impact" and accordingly the reference does not teach the administration of allopregnanolone following a traumatic brain injury as recited in claims 1-7 and 12-13 ". Applicant's argument is not found persuasive. As discussed above, Note that seizures are known to

be resulted from traumatic brain injury (see Hernandez et al., *Seizures, epilepsy, and functional recovery after traumatic brain injury: a reappraisal*, of record).

Thus, Tauboll's method steps are same as the instant method steps, administering the same compound in the same amount to the same or similar or substantially overlapping patient population having seizures after traumatic brain injury.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 102(b). Therefore, said rejection is adhered to.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Roof et al. or Gee et al. in view of Weinshenker et al. (5,068,226) for same reasons of record stated in the Office Action dated November 4, 2004.

The same disclosure of Roof et al. or Gee et al. has been discussed in the 102(b) rejection set forth above.

The prior art does not expressly disclose the employment of cyclodextrin as the carrier for the particular progesterone metabolite, allopregnanolone.

Weinshenker et al. discloses that cyclodextrins are broadly known to be useful as carriers for improving the delivery of active agents such as steroids, e.g., cyclodextrins enhancing the solubility of progesterone 2000 fold and similar effects are observed with other steroids such as prednisolone (see col.6 lines 20-32).

One having ordinary skill in the art at the time the invention was made would have been motivated to employ cyclodextrin as the carrier for the particular progesterone metabolite, allopregnanolone since that cyclodextrins are broadly known to be useful as carriers for improving the delivery of active agents such as steroids, e.g., cyclodextrins enhancing the solubility of progesterone 2000 fold and similar effects are observed with other steroids such as prednisolone according to Weinshenker et al.

Applicant's same or substantially similar arguments as the 102 rejections above with respect to this rejection made under 35 U.S.C. 103(a) in the previous Office Action have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as discussed above.

In view of the rejections to the pending claims set forth above, no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner
Art Unit 1617
June 14, 2005